

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number  
**WO 00/75136 A1**

(51) International Patent Classification<sup>7</sup>: C07D 405/12, 417/12, A61K 31/4164, A61P 9/08

(74) Agent: VERBERCKMOES, Filip; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(21) International Application Number: PCT/EP00/04746

(22) International Filing Date: 23 May 2000 (23.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(28) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(30) Priority Data: 99201747.5 2 June 1999 (02.06.1999) EP

(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Department, Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VAN EMELEN, Kristof [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE BRUYN, Marcel, Frans, Leopold [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

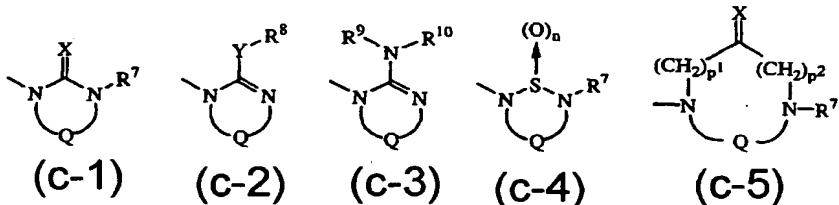
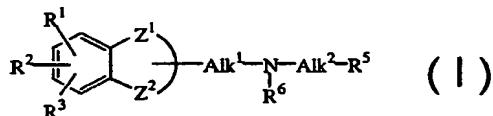
(81) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

[Continued on next page]

(54) Title: AMINOALKYL SUBSTITUTED (BENZODIOXAN, BENZOFURAN OR BENZOPYRAN) DERIVATIVES



(c-1)

(c-2)

(c-3)

(c-4)

(c-5)

A1

WO 00/75136

(57) Abstract: The present invention concerns compounds of formula (I), a stereochemically isomeric form thereof, an N-oxide form thereof or a pharmaceutically acceptable acid addition salt thereof, wherein -Z<sup>1</sup>-Z<sup>2</sup>- is a bivalent radical; R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently selected from hydrogen, C<sub>1-6</sub>alkyl, hydroxy, halo and the like; or when R<sup>1</sup> and R<sup>2</sup> are on adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> taken together may form a bivalent radical of formula; Alk<sup>1</sup> and Alk<sup>2</sup> are optionally substituted C<sub>1-6</sub>alkanediyl; R<sup>6</sup> is hydrogen or phenylmethyl; R<sup>5</sup> is a radical of formulae (c-1), (c-2), (c-3), (c-4), (c-5); wherein n is 1 or 2; p<sup>1</sup> is 0, and p<sup>2</sup> is 1 or 2; or p<sup>1</sup> is 1 or 2, and p<sup>2</sup> is 0; X is oxygen, sulfur or =NR<sup>9</sup>; Y is oxygen or sulfur; R<sup>7</sup> is hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, phenyl or phenylmethyl; R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl phenyl or phenylmethyl; R<sup>9</sup> is cyano, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cyclo-alkyl, C<sub>1-6</sub>alkyloxycarbonyl or aminocarbonyl; R<sup>10</sup> is hydrogen or C<sub>1-6</sub>alkyl; and Q is a bivalent radical. Processes for preparing said products, formulations comprising said products and their use as a medicine are disclosed, in particular for treating conditions which are related to impaired fundic relaxation.

WO 00/75136 A1



*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

AMINOALKYL SUBSTITUTED (BENZODIOXAN, BENZOFURAN  
OR BENZOPYRAN) DERIVATIVES

---

5 The present invention is concerned with novel aminoalkylchromane compounds having fundic relaxation properties. The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds.

10 Structurally related aminomethylchromane derivatives are disclosed in US-5,541,199 as selective autoreceptor agonists useful as antipsychotic agents. Other structurally related aminomethylchroman derivatives having affinity for cerebral 5-hydroxytryptamine receptors of the 5-HT<sub>1</sub> type and therefore suitable for the treatment of disorders of the central nervous system are disclosed in US-5,137,901.

15 EP-0,546,388, published on 16 June 1993, discloses structurally related amino-methylchroman derivatives having affinity for cerebral 5-hydroxytryptamine receptors of the 5-HT<sub>1</sub> type and for dopamine receptors of the D<sub>2</sub>-type. EP-0,628,310, published on 14 December 1994, encompasses the use of the same aminomethylchroman derivatives for the inhibition of HIV-protease.

20 DE-2,400,094, published on 18 July 1974, discloses 1-[1-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-4-piperidyl-2-benzimidazolinones possessing blood pressure lowering activity.

25 DE-2,852,945, published on 26 June 1980, discloses benzodioaxanylhydroxyethyl-piperidylimidazolidinones having antihypertensive activity.

30 EP-0,004,358, published on 3 October 1979, discloses *N*-oxacycloalkylalkylpiperidines useful as antidepressants and psychostimulants.

35 EP-0,048,218, published on 24 March 1982, discloses *N*-oxides of *N*-oxacycloalkyl-alkylpiperidines having antidepressant activity.

WO-93/17017, published on 2 September 1993, discloses [(benzodioxane, benzofuran or benzopyran)alkylamino]alkyl-substituted guanidine as selective vasoconstrictors useful to treat conditions related to vasodilatation such as, e.g., migraine, cluster headache and headache associated with vascular disorders.

-2-

WO-95/053837, published on 23 February 1995, encompasses dihydrobenzopyran-pyrimidine derivatives also having vasoconstrictive activity.

Other structurally related aminomethylchroman derivatives are disclosed in

5 WO-97/28157, published on 7 August 1997, as  $\alpha_2$ -adrenergic receptor antagonists useful in the treatment of degenerative neurological conditions.

The compounds of the present invention differ from the cited art-known compounds structurally, by the nature of the  $R^5$  substituent, and pharmacologically by the fact that,

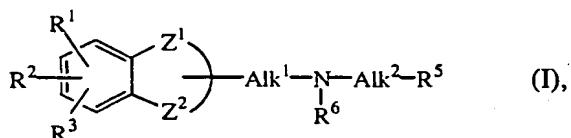
10 unexpectedly, these compounds have fundic relaxation properties. Furthermore, the compounds of the present invention have additional beneficial pharmacological properties in that they have little or no vasoconstrictor activity.

During the consumption of a meal the fundus, *i.e.* the proximal part of the stomach,

15 relaxes and provides a "reservoir" function. Patients having an impaired adaptive relaxation of the fundus upon food ingestion have been shown to be hypersensitive to gastric distension and display dyspeptic symptoms. Therefore, it is believed that compounds which are able to normalize an impaired fundic relaxation are useful to relieve patients suffering from said dyspeptic symptoms.

20

The present invention concerns compounds of formula (I)



25 a stereochemically isomeric form thereof, an *N*-oxide form thereof, a pharmaceutically acceptable acid addition salt thereof, or a quaternary ammonium salt thereof, wherein Alk<sup>1</sup> is C<sub>1</sub>-4alkylcarbonyl, C<sub>1</sub>-4alkylcarbonylC<sub>1</sub>-4alkyl, carbonyl, carbonylC<sub>1</sub>-4alkyl, or C<sub>1</sub>-6alkanediyl optionally substituted with hydroxy, halo, amino, hydroxyC<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkyloxy, C<sub>1</sub>-4alkyloxyC<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkylcarbonyloxy, C<sub>1</sub>-4alkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyloxy, or C<sub>3</sub>-6cycloalkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyloxy;

30 Alk<sup>2</sup> is C<sub>1</sub>-4alkylcarbonylC<sub>1</sub>-4alkyl; C<sub>1</sub>-6alkanediyl substituted with hydroxy, halo, amino, hydroxyC<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkyloxy, C<sub>1</sub>-4alkyloxyC<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkyloxycarbonyl, C<sub>1</sub>-4alkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyloxy, or C<sub>3</sub>-6cycloalkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyloxy; C<sub>3</sub>-8cycloalkanediyl

35 optionally substituted with halo, hydroxy, hydroxyC<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkyloxy,

-3-

C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy, or C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy;

-Z<sup>1</sup>-Z<sup>2</sup>- is a bivalent radical of formula

5	-O-CH(R <sup>4</sup> )-CH <sub>2</sub> -	(a-1),
	-O-CH(R <sup>4</sup> )-CH <sub>2</sub> -O-	(a-2),
	-O-CH(R <sup>4</sup> )-CH <sub>2</sub> -S-	(a-3),
	-O-CH(R <sup>4</sup> )-CH <sub>2</sub> -CH <sub>2</sub> -	(a-4),
	-O-CH(R <sup>4</sup> )-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(a-5),
10	-O-C(R <sup>4</sup> )=CH-	(a-6),
	-O-C(R <sup>4</sup> )=CH-CH <sub>2</sub> -	(a-7),
	-O-C(R <sup>4</sup> )=CH-CH <sub>2</sub> -CH <sub>2</sub> -	(a-8), or
	-O-CH(R <sup>4</sup> )-CH=CH-	(a-9).

15 wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy;

$R^1$ ,  $R^2$  and  $R^3$  are each independently selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>1-6</sub>alkyloxy, trihalomethyl, trihalomethoxy, halo, hydroxy, cyano, nitro, amino, C<sub>1-6</sub>alkylcarbonylamino, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxy, aminocarbonyl, mono- or di(C<sub>1-6</sub>alkyl)aminocarbonyl, aminoC<sub>1-6</sub>alkyl, mono- or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy, or C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy; or

when  $R^1$  and  $R^2$  are on adjacent carbon atoms,  $R^1$  and  $R^2$  taken together may form a bivalent radical of formula

25	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-1),	-O-CH <sub>2</sub> -CH <sub>2</sub> -	(b-6),
	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-2),	-O-CH <sub>2</sub> -CH <sub>2</sub> -O-	(b-7),
	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-3),	-O-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-8),
	-CH=CH-CH=CH-	(b-4),	-O-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-9),
	-O-CH <sub>2</sub> -O-	(b-5),		

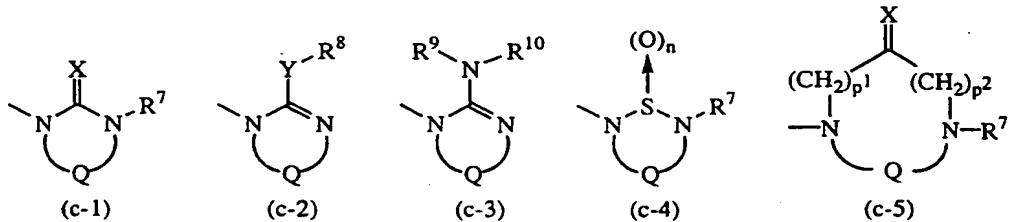
30 wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy,  $C_1-C_4$ alkyl or  $CH_2OH$ ;

R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, phenylmethyl, hydroxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyl, C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy, or a direct bond when the bivalent radical -Z<sup>1</sup>-Z<sup>2</sup>- is of formula (a-6), (a-7) or (a-8):

35 R<sup>6</sup> is hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, phenylmethyl, C<sub>1-4</sub>alkylaminocarbonyl, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyl, or C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy;

-4-

$R^5$  is a radical of formula



wherein n is 1 or 2;

5  $p^1$  is 0, and  $p^2$  is 1 or 2; or  $p^1$  is 1 or 2, and  $p^2$  is 0;

$X$  is oxygen, sulfur,  $NR^9$  or  $CHNO_2$ ;

$Y$  is oxygen or sulfur;

$R^7$  is hydrogen,  $C_1$ -6alkyl,  $C_3$ -6cycloalkyl, phenyl or phenylmethyl;

$R^8$  is  $C_1$ -6alkyl,  $C_3$ -6cycloalkyl, phenyl or phenylmethyl;

10  $R^9$  is cyano,  $C_1$ -6alkyl,  $C_3$ -6cycloalkyl,  $C_1$ -6alkyloxycarbonyl or aminocarbonyl;

$R^{10}$  is hydrogen or  $C_1$ -6alkyl;

or  $R^9$  and  $R^{10}$  taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, or morpholinyl group, optionally substituted with  $C_1$ -4alkyl or  $C_1$ -4alkyloxy; and

15  $Q$  is a bivalent radical of formula

- $CH_2-CH_2-$  (d-1),  $-CO-CH_2-$  (d-6),

- $CH_2-CH_2-CH_2-$  (d-2),  $-(CH_2)_2-CO-$  (d-7),

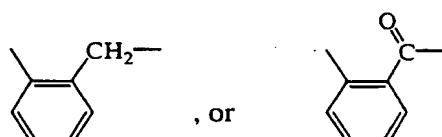
- $CH_2-CH_2-CH_2-CH_2-$  (d-3),  $-CO-(CH_2)_2-$  (d-8),

- $CH=CH-$  (d-4),  $-CO-CH_2-CO-$  (d-9),

20 - $CH_2-CO-$  (d-5),  $-CH_2-CO-CH_2-$  (d-10),

wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by  $C_1$ -4alkyl, hydroxy or phenyl, or

$Q$  is a bivalent radical of formula



25

(d-11)

(d-12)

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo;  $C_1$ -4alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-

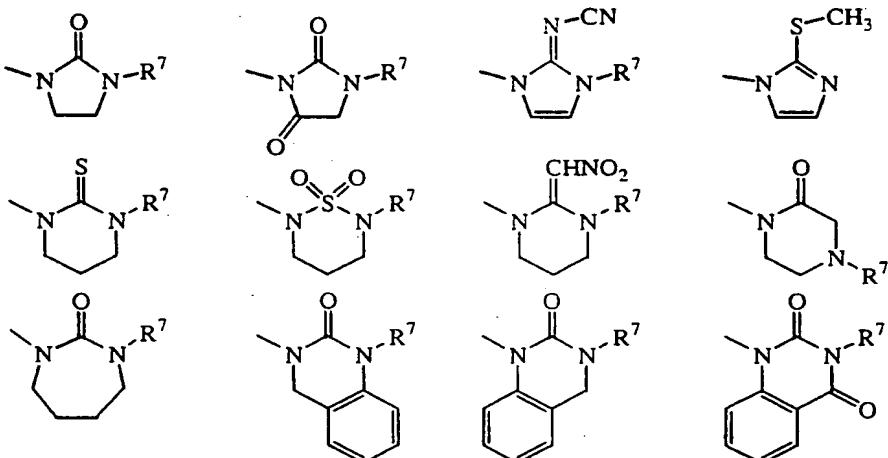
-5-

ethyl, 2-methylpropyl and the like; C<sub>1-6</sub>alkyl is meant to include C<sub>1-4</sub>alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like; C<sub>3-6</sub>cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C<sub>3-6</sub>alkenyl defines straight and branched chain

5 unsaturated hydrocarbon radicals having from 3 to 6 carbon atoms, such as propenyl, butenyl, pentenyl or hexenyl; C<sub>1-2</sub>alkanediyl defines methylene or 1,2-ethanediyl; C<sub>1-3</sub>alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 3 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, and the branched isomers thereof; C<sub>1-5</sub>alkanediyl defines bivalent  
 10 straight or branched chain hydrocarbon radicals containing from 1 to 5 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, and the branched isomers thereof; C<sub>1-6</sub>alkanediyl includes C<sub>1-5</sub>alkanediyl and the higher homologues thereof having 6 carbon atoms such as, for example, 1,6-hexanediyl and the like. The term "CO" refers to a carbonyl group.

15

Some examples of the R<sup>5</sup> moiety are :



20

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all

25 diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration.

Compounds encompassing double bonds can have an E or Z-stereochemistry at said

double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

In compounds of formula (I) wherein the bivalent radical  $-Z^1-Z^2-$  is of formula (a-6),  
5 (a-7) or (a-8) the substituent  $R^4$  is a direct bond to the  $-Alk^1-NR^6-Alk^2-R^5$  moiety.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid 10 addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid),  
15 maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into 20 the free base form.

Quaternary ammonium salts of compounds of formula (I) as used herein defines which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, 25 an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl *p*-toluenesulfonates. A quaternary ammonium salt has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The 30 counterion of choice can be made using ion exchange resin columns.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

35 The *N*-oxide forms of the compounds of formula (I), which may be prepared in art-known manners, are meant to comprise those compounds of formula (I) wherein a nitrogen atom is oxidized to the *N*-oxide.

Interesting compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

- a) the bivalent radical  $-Z^1-Z^2-$  is of formula (a-1), or (a-6); or
- b) the bivalent radical  $-Z^1-Z^2-$  is of formula (a-2), (a-3), (a-4), or (a-9); in particular
- 5        the bivalent radical  $-Z^1-Z^2-$  is of formula (a-3) or (a-4); or
- c) the bivalent radical  $-Z^1-Z^2-$  is of formula (a-4);
- d)  $R^1$ ,  $R^2$  and  $R^3$  are each independently selected from hydrogen,  $C_{1-6}$ alkyl, hydroxy or halo;
- e)  $R^4$  is hydrogen;
- 10    f)  $Alk^1$  is  $C_{1-2}$ alkanediyl optionally substituted with hydroxy, in particular  $Alk^1$  is  $-CH_2-$ ;
- g)  $Alk^2$  is  $C_{1-3}$ alkanediyl substituted with hydroxy, in particular  $Alk^2$  is  $-CH_2-CHOH-CH_2-$ ; and/or
- h)  $R^6$  is hydrogen of phenylmethyl.

15

Particular compounds of formula (I) are those compounds of formula (I) wherein the bivalent radical  $-Z^1-Z^2-$  is of formula  $-CH_2-CH_2-$  (a-4).

Preferred compounds are those compounds of formula (I) wherein  $R^5$  is a radical of

20    formula (c-1) wherein X is oxygen, and Q is a radical of formula (d-2) or (d-5).

More preferred compounds are those compounds of formula (I) wherein  $R^4$  is hydrogen;  $Alk^1$  is  $-CH_2-$ ;  $Alk^2$  is  $-CH_2-CHOH-CH_2-$ ;  $R^6$  is hydrogen;  $R^5$  is a radical of

25    formula (c-1) wherein X is oxygen,  $R^7$  is hydrogen, and Q is (d-2).

25

Other more preferred compounds are those compounds of formula (I) wherein  $R^4$  is hydrogen;  $Alk^1$  is  $-CH_2-$ ;  $Alk^2$  is  $-CH_2-CHOH-CH_2-$ ;  $R^6$  is hydrogen;  $R^5$  is a radical of

formula (c-1) wherein X is oxygen,  $R^7$  is hydrogen, and Q is (d-5).

30

Still other preferred compounds are those compounds of formula (I) wherein  $R^4$  is hydrogen;  $Alk^1$  is  $-CHOH-CH_2-$ ;  $Alk^2$  is  $-CH_2-CHOH-CH_2-$ ;  $R^6$  is hydrogen;  $R^5$  is a radical of formula (c-1) wherein X is oxygen,  $R^7$  is hydrogen, and Q is (d-2).

Most preferred compound is

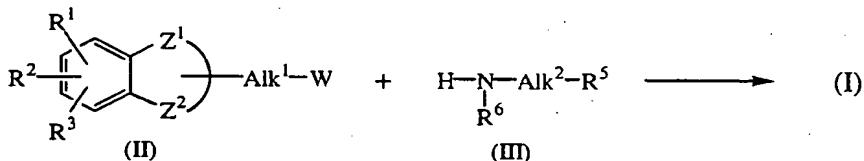
35    1-[3-[[3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]-2-hydroxypropyl]-2,4-imidazolidinedione; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

The compounds of the present invention can generally be prepared by alkylating an

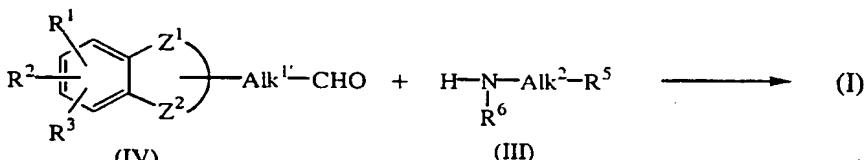
intermediate of formula (III) with an intermediate of formula (II), wherein W is an appropriate leaving group such as, for example, halo, e.g. fluoro, chloro, bromo, iodo, or in some instances W may also be a sulfonyloxy group, e.g. methanesulfonyloxy, benzenesulfonyloxy, trifluoromethanesulfonyloxy and the like reactive leaving groups.

5 The reaction can be performed in a reaction-inert solvent such as, for example, acetonitrile or tetrahydrofuran, and optionally in the presence of a suitable base such as, for example, sodium carbonate, potassium carbonate, calcium oxide or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and the reflux temperature of the reaction mixture and, if desired, the reaction may be carried out in an autoclave at an increased pressure.

10



15 Compounds of formula (I) can also be prepared by reductively alkylating an intermediate of formula (IV), wherein Alk<sup>1</sup> represents a direct bond or C<sub>1-5</sub>alkanediyl, following art-known reductive alkylation procedures with an intermediate of formula (III).



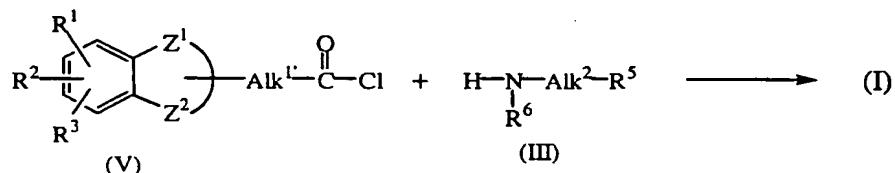
20 (IV) (III)

Said reductive alkylation can be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol, toluene or a mixture thereof, and in the presence of a reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal, rhodium-on-carbon or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. To enhance the rate of the

-9-

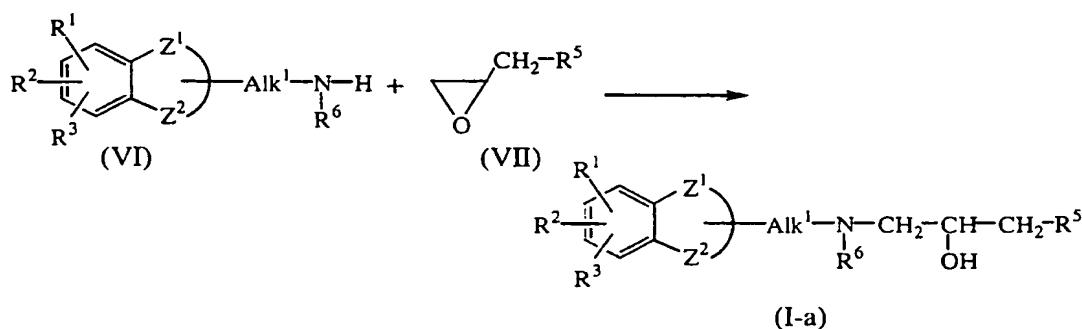
reaction, the temperature may be elevated in a range between room temperature and the reflux temperature of the reaction mixture and optionally the pressure of the hydrogen gas may be raised.

5 Alternatively, compounds of formula (I) can also be prepared by reacting an acid chloride of formula (V), wherein  $\text{Alk}^1$  represents  $\text{C}_1\text{-salkanediyl}$  or a direct bond, with an intermediate of formula (III) under suitable reaction conditions.



10 Said reaction can be performed under hydrogenation conditions with hydrogen gas in the presence of a suitable catalyst such as, for example, palladium-on-charcoal, rhodium-on-carbon or platinum-on-charcoal, in a suitable solvent such as, for example, ethyl acetate, and in the presence of magnesium oxide. In order to prevent the undesired 15 further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g. thiophene or quinoline-sulphur. To enhance the rate of the reaction, the temperature may be elevated in a range between room temperature and the reflux temperature of the reaction mixture and optionally the pressure of the hydrogen 20 gas may be raised.

Compounds of formula (I-a), defined as compounds of formula (I) wherein  $\text{Alk}^2$  represents  $-\text{CH}_2-\text{CHOH}-\text{CH}_2-$ , can be prepared by reacting intermediates of formula (VI) with intermediates of formula (VII) in a reaction-inert solvent, such as methanol, 25 and optionally in the presence of an organic base, such as triethyl amine.



-10-

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions. For instance, compounds of formula (I) wherein R<sup>6</sup> is phenylmethyl can be converted to the corresponding compounds of formula (I) wherein R<sup>6</sup> is hydrogen by art-known

5 debenzylation procedures. Said debenzylation can be performed following art-known procedures such as catalytic hydrogenation using appropriate catalysts, e.g. platinum on charcoal, palladium on charcoal, in appropriate solvents such as methanol, ethanol, 2-propanol, diethyl ether, tetrahydrofuran, and the like. Furthermore, compounds of formula (I) wherein R<sup>6</sup> is hydrogen may be alkylated using art-known procedures such as, e.g. reductive *N*-alkylation with a suitable aldehyde or ketone.

10 The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the

15 starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarbo-peroxoic acid or halo substituted benzenecarboperoxoic acid, e.g.

20 3-chlorobenzene-carboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

25 The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, a number of intermediates of formula (II) or (V) may be prepared according to art-known methodologies

30 described in WO-93/17017 and WO-95/053837.

35 Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration, such as, e.g. the carbon atom bearing the R<sup>4</sup> substituent, and the carbon atom linked to the -Alk<sup>1</sup>-NR<sup>6</sup>-Alk<sup>2</sup>-R<sup>5</sup> moiety.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated

from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are 5 liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific 10 stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the *N*-oxide forms, the pharmaceutically acceptable salts 15 and stereoisomeric forms thereof possess favourable fundic relaxation properties as evidenced in pharmacological example C-1, the "Gastric tone measured by an electronic barostat in conscious dogs"-test.

Furthermore, the compounds of the present invention have additional beneficial 20 pharmacological properties in that they have little or no vasoconstrictor activity as can be demonstrated in pharmacological example C.2 "Vasoconstrictive activity on basilar artery". Vasoconstrictor activity can cause undesirable side-effects such as coronary effects which can induce chest pain.

25 In view of the capability of the compounds of the present invention to relax the fundus, the subject compounds are useful to treat conditions related to a hampered or impaired relaxation of the fundus such as, e.g. dyspepsia, early satiety, bloating and anorexia.

Dyspepsia is described as a motility disorder. Symptoms can be caused by a delayed 30 gastric emptying or by impaired relaxation of the fundus to food ingestion. Warm-blooded animals, including humans, (generally called herein patients) suffering from dyspeptic symptoms as a result of delayed gastric emptying usually have a normal fundic relaxation and can be relieved of their dyspeptic symptoms by administering a prokinetic agent such as, e.g. cisapride. Patients can have dyspeptic symptoms without 35 having a disturbed gastric emptying. Their dyspeptic symptoms may result from a hypercontracted fundus or hypersensitivity resulting in a diminished compliance and abnormalities in the adaptive fundic relaxation. A hypercontracted fundus results in a diminished compliance of the stomach. The "compliance of the stomach" can be

expressed as the ratio of the volume of the stomach over the pressure exerted by the stomach wall. The compliance of the stomach relates to the gastric tone, which is the result of the tonic contraction of muscle fibers of the proximal stomach. This proximal part of the stomach, by exerting a regulated tonic contraction (gastric tone),  
5 accomplishes the reservoir function of the stomach.

Patients suffering from early satiety cannot finish a normal meal since they feel  
saturated before they are able to finish said normal meal. Normally when a subject  
starts eating, the stomach will show an adaptive relaxation, *i.e.* the stomach will relax to  
10 accept the food that is ingested. This adaptive relaxation is not possible when the  
compliance of the stomach is hampered which results in an impaired relaxation of the  
fundus.

In view of the utility of the compounds of formula (I), it follows that the present  
15 invention also provides a method of treating warm-blooded animals, including humans,  
(generally called herein patients) suffering from impaired relaxation of the fundus to  
food ingestion. Consequently a method of treatment is provided for relieving patients  
suffering from conditions, such as, for example, dyspepsia, early satiety, bloating and  
20 anorexia.

20 Hence, the use of a compound of formula (I) as medicine is provided, and in particular  
the use of a compound of formula (I) for the manufacture of a medicine for treating  
conditions involving an impaired relaxation of the fundus to food ingestion. Both  
prophylactic and therapeutic treatment are envisaged.

25 The symptoms of impaired fundic relaxation may also arise due to the intake of  
chemical substances, *e.g.* Selective Serotonin Re-uptake Inhibitors (SSRI's), such as  
fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline.

30 To prepare the pharmaceutical compositions of this invention, an effective amount of  
the particular compound, in base or acid addition salt form, as the active ingredient is  
combined in intimate admixture with a pharmaceutically acceptable carrier, which  
carrier may take a wide variety of forms depending on the form of preparation desired  
for administration. These pharmaceutical compositions are desirably in unitary dosage  
35 form suitable, preferably, for administration orally, rectally or by parenteral injection.  
For example, in preparing the compositions in oral dosage form, any of the usual  
pharmaceutical media may be employed, such as, for example, water, glycols, oils,  
alcohols and the like in the case of oral liquid preparations such as suspensions, syrups,

-13-

elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are

5 obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate

10 liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin

15 and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

20 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association

25 with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

30 For oral administration, the pharmaceutical compositions may take the form of solid dose forms, for example, tablets (both swallowable-only and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose,

35 microcrystalline cellulose or calcium phosphate); lubricants e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting

-14-

agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, 5 solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means, optionally with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxy-propyl methylcellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or 10 acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame 15 potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

20 Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, and preferably is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener 25 can effectively be used in larger quantities ranging from about 10% to about 35%, preferably from about 10% to 15% (w/v).

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients 30 in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two flavours may yield very good results. In the high-dosage formulations stronger flavours may be required such as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like 35 pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1% (w/v). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and colour under the acidic conditions of the formulation.

-15-

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials

5 (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for

10 example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as isotonizing, suspending, stabilising and/or dispersing agents.

15 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such

20 as cocoa butter or other glycerides.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

25 The formulations of the present invention may optionally include an anti-flatulent, such as simethicone, alpha-D-galactosidase and the like.

In general it is contemplated that a therapeutically effective amount would be from about 0.001 mg/kg to about 2 mg/kg body weight, preferably from about 0.02 mg/kg to 30 about 0.5 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

#### Experimental part

In the procedures described hereinafter the following abbreviations were used : "ACN"

35 stands for acetonitrile and "DCM" stands for dichloromethane.

For some chemicals the chemical formula was used, e.g.  $\text{CH}_2\text{Cl}_2$  for dichloromethane,  $\text{CH}_3\text{OH}$  for methanol,  $\text{NH}_3$  for ammonia,  $\text{HCl}$  for hydrochloric acid, and  $\text{NaOH}$  for sodium hydroxide.

In those cases the stereochemically isomeric form which was first isolated is designated as "A", the second as "B", the third one as "C" and the fourth one as "D", without further reference to the actual stereochemical configuration.

5

A. Preparation of the intermediates

Example A.1

A reaction solution of 1-(2-propenyl)-2,4-imidazolidinedione (0.036 mol) and 3-chlorobenzenecarboperoxoic acid (0.043 mol, 70.75%) in DCM (25 ml) was stirred for

10 2 hours at room temperature. An aqueous solution of bisulfite was added (to remove excess 3-chlorobenzenecarboperoxoic acid) and the mixture was stirred for 10 minutes. Na<sub>2</sub>CO<sub>3</sub> was added and this mixture was extracted with DCM. The separated organic layer was dried, filtered and the solvent evaporated, yielding 5 g (89%) of (±)-1-(oxiranylmethyl)-2,4-imidazolidinedione (interm. 1).

15

Example A.2

a) A solution of 2-hydroxypyrimidine hydrochloride (1:1) (0.075 mol) in methanol (150 ml) was stirred for 30 minutes and then added to a solution of sodium carbonate (0.075 mol) in methanol (20 ml). The mixture was stirred and refluxed for 15 minutes,

20 and cooled to 55°C. A solution of *N,N*-bis(phenylmethyl)oxiranmethanamine (0.075 mol) in toluene (160 ml) was added dropwise and the reaction mixture was stirred at 50°C overnight. Water (75 ml) was added and the mixture was stirred at 55°C for 15 minutes. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over 25 silica gel (eluent: CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> 97/3). The pure fractions were collected and the solvent was evaporated, yielding 11.8 g (45%) of (±)-1-[3-[bis(phenylmethyl)amino]-2-hydroxypropyl]-2(1*H*)pyrimidinone (interm. 2).

30 b) A solution of intermediate (2) (0.034 mol) in methanol (500 ml) was hydrogenated with palladium on activated carbon as a catalyst in the presence of thiophene. After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/(CH<sub>3</sub>OH/NH<sub>3</sub>) 95/5). The pure fractions were collected and the solvent was evaporated, yielding 6.15 g (70%) of tetrahydro-1-[2-hydroxy-3-[(phenylmethyl)amino]propyl]-2(1*H*)pyrimidinone (interm. 3).

35

B. Preparation of the final compoundsExample B.1

3,4-Dihydro-*N*-(phenylmethyl)-2*H*-1-benzopyran-2-methanamine (0.032 mol) in methanol (100 ml) was stirred at room temperature. A solution of intermediate (1) (0.032 mol) in methanol (50 ml) was added dropwise and the resulting reaction mixture was stirred overnight at room temperature. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$  99/1). The desired fractions were collected and the solvent was evaporated, yielding 3.5g (27%) of ( $\pm$ )-1-[3-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl](phenylmethyl)-amino]-2-hydroxypropyl]-2,4-imidazolidinedione (comp. 3).

Example B.2

A mixture of 3,4-dihydro-2*H*-1-benzopyran-2-carboxaldehyde, (0.023 mol) and intermediate (3) (0.023 mol) in methanol (250 ml) was hydrogenated with palladium on activated carbon (10%) as a catalyst in the presence of thiophene. After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent :  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  99/1). The pure fractions were collected and the solvent was evaporated, yielding 5.9 g (62%) of ( $\pm$ )-1-[3-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl](phenylmethyl)amino]-2-hydroxypropyl]tetrahydro-2(1*H*)pyrimidinone (comp. 1).

Example B.3

A mixture of compound (3) (0.0086 mol) in methanol (100 ml) was hydrogenated at 25°C with palladium on activated carbon (1 g) as a catalyst. After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in ACN and converted into the hydrochloric acid salt (1:1) with HCl/2-propanol. The precipitate was filtered off and dried, yielding 0.49 g of ( $\pm$ )-1-[3-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]amino]-2-hydroxypropyl]-2,4-imidazolidinedione monohydrochloride (comp. 4).

Example B.4

a) A solution of 2-hydroxypyrimidine (0.16 mol) in methanol (300 ml) was stirred at room temperature for 30 minutes. A solution of  $\text{Na}_2\text{CO}_3$  (0.16 mol) in methanol (40 ml) was added. The mixture was stirred and refluxed for 15 minutes and cooled to 55°C. A solution of *N,N*-bis(phenylmethyl)-2-oxiranemethanamine (0.16 mol) in toluene (320 ml) was added dropwise. The mixture was stirred at 50°C overnight. Water (150 ml) was added. The mixture was stirred at 55°C for 15 minutes. The organic layer

-18-

was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent :

CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 97/3). The pure fractions were collected and the solvent was evaporated, yielding 26.55g of (±)-1-[3-[bis(phenylmethyl)amino]-2-hydroxypropyl]-

5 2(1*H*)pyrimidinone (intermediate 4).

b) A mixture of intermediate (4) (0.073 mol) in HCl/2-propanol (20 ml) and CH<sub>3</sub>OH (250 ml) was hydrogenated with Pd/C 10% (2 g) as a catalyst. After uptake of hydrogen (3 equivalents), the catalyst was filtered off and the filtrate was evaporated. The residue was separated into its enantiomers by HPLC (eluent : hexane/EtOH 50/50; Chiralpak

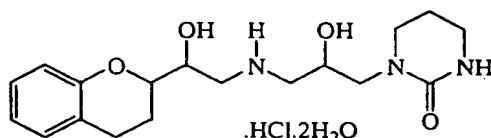
10 AD 1000 Å 20 µm). The pure fractions were collected and the solvent was evaporated, yielding 4 g of (A)-tetrahydro-1-[2-hydroxy-3-[(phenylmethyl)amino]propyl]-2(1*H*)-pyrimidinone (intermediate 5).

c) A mixture of [S-(R\*,R\*)]-3,4-dihydro-2-oxiranyl-2*H*-1-benzopyran (0.006 mol) and intermediate (5) (0.006 mol) in ethanol (25 ml) was stirred and refluxed for 2 hours.

15 The solvent was evaporated and the residue was purified by HPLC (eluent : hexane/ethanol 70/30; Chiralcel OJ 20 µm). The pure fractions were collected and the solvent was evaporated, yielding 1.7 g of [S(A)]-1-[3-[[2-(3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-hydroxy ethyl](phenylmethyl)amino]-2-hydroxypropyl]tetrahydro-2(1*H*)-pyrimidinone (intermediate 6).

20 d) A mixture of intermediate (6) (0.004 mol) in CH<sub>3</sub>OH (100 ml) was hydrogenated with Pd/C 10% (0.5 g) as a catalyst. After uptake of hydrogen (1 equivalent), the catalyst was filtered off. The reaction mixture was converted into the hydrochloric acid salt (1:1) with HCl/2-propanol. DIPE was added. The precipitate was filtered off and dried, yielding 0.69 g of [S(A)]-1-[3-[[2-(3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-

25 hydroxy ethyl]amino]-2-hydroxypropyl]tetrahydro-2(1*H*)-pyrimidinone monohydrochloride dihydrate (mp. 138°C) (compound 15).



compound 15

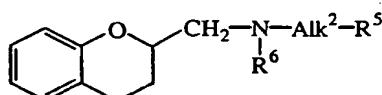
30 Table F-1 and F-2 list the compounds that were prepared according to one of the above Examples and table F.3 lists both the experimental (column heading "exp.") and theoretical (column heading "theor.") elemental analysis values for carbon, hydrogen

-19-

and nitrogen of some of the compounds as prepared in the experimental part hereinabove.

Table F-1

5



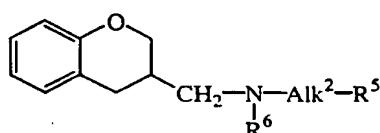
Co No.	Ex. No.	R <sup>6</sup>	—Alk <sup>2</sup> —R <sup>5</sup>	Physical data (mp. in °C)
1	B.2	-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>		-
2	B.3	H		.HCl (1:2)
3	B.1	-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>		-
4	B.3	H		.HCl (1:1)
5	B.3	H		(A); .HCl (1:2)
6	B.3	H		(B); .HCl (1:1)
7	B.3	H		(C); .HCl (1:2)
8	B.3	H		(D); .HCl (1:1) .H <sub>2</sub> O (1:1)
13	B.1	-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>		(R); .HCl (1:1)

-20-

Co No.	Ex. No.	R <sup>6</sup>	—Alk <sup>2</sup> —R <sup>5</sup>	Physical data (mp. in °C)
14	B.3	H	$-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{N}(\text{H})\text{C}(=\text{O})\text{C}(\text{O})\text{N}$	(R); .HCl (1:1); mp. 241°C; $[\alpha]_D^{20} = -75.62^\circ$ , $c = 4.95 \text{ mg/ml in CH}_3\text{OH}$

.C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> stands for the ethanedioate salt

Table F-2



5

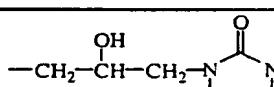
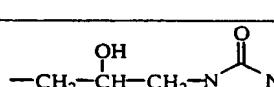
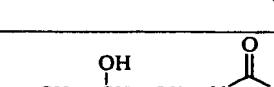
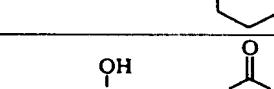
Co. No.	Ex. No.	R <sup>6</sup>	—Alk <sup>2</sup> —R <sup>5</sup>	Physical data (mp. in °C)
9	B.1	-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>		.HCl (1:1)
10	B.3	H		.HCl (1:1)
11	B.2	-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>		-
12	B.3	H		-

Table F.3 :

10

Co. No.	Carbon		Hydrogen		Nitrogen	
	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
2	53.30	52.05	7.11	6.94	11.04	10.71
4	52.82	54.01	5.95	6.23	11.34	11.81
5	53.29	52.04	7.60	6.94	10.32	10.71
6	53.94	57.38	7.34	7.36	11.06	11.81
7	52.85	52.04	7.90	6.94	10.15	10.71
8	53.22	54.61	7.65	7.55	10.87	11.24

Co. No.	Carbon		Hydrogen		Nitrogen	
	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
10	53.52	54.01	6.14	6.23	11.63	11.81
12	57.44	57.38	7.31	7.36	11.61	11.81

C. Pharmacological examples

C.1. Gastric tone measured by an electronic barostat in conscious dogs

5 Gastric tone cannot be measured by manometric methods. Therefore an electronic barostat was used. This allows the study of the physiological pattern and regulation of gastric tone in conscious dogs and the influence of test-compounds on this tone.

The barostat consists of an air injection system which is connected by a double-lumen 14-French polyvinyl tube to an ultrathin flaccid polyethylene bag (maximal volume: 10  $\pm$  700 ml). Variations in gastric tone were measured by recording changes in the volume of air within an intragastric bag, maintained at a constant pressure. The barostat maintains a constant pressure (preselected) within a flaccid air-filled bag introduced into the stomach, changing the volume of air within the bag by an electronic feedback system.

15 Thus, the barostat measures gastric motor activity (contraction or relaxation) as changes in intragastric volume (decrease or increase resp.) at a constant intragastric pressure. The barostat consists of a strain gauge linked by an electronic relay to an air injection-aspiration system. Both the strain gauge and the injection system are connected by 20 means of double-lumen polyvinyl tube to an ultrathin polyethylene bag. A dial in the barostat allows selection of the pressure level to be maintained within the intragastric bag.

Female beagle dogs, weighing 7-17 kg, were trained to stand quietly in Pavlov frames. 25 They were implanted with a gastric cannula under general anaesthesia and aseptic precautions. After a median laparotomy, an incision was made through the gastric wall in longitudinal direction between the greater and the lesser curve, 2 cm above the nerves of Latarjet. The cannula was secured to the gastric wall by means of a double purse string suture and brought out via a stub wound at the left quadrant of the 30 hypochondrium. Dogs were allowed a recovery period of two weeks.

At the beginning of the experiment, the cannula was opened in order to remove any gastric juice or food remnants. If necessary, the stomach was cleansed with 40 to 50 ml lukewarm water. The ultrathin bag of the barostat was positioned into the fundus of the

stomach through the gastric cannula. In order to ensure easy unfolding of the intragastric bag during the experiment, a volume of 300-400 ml was injected twice into the bag.

5 When during a stabilisation period of maximum 90 minutes, the gastric volume is stable during 15 minutes at a constant pressure of 6 mmHg (about 0.81 kPa), the test compound was administered subcutaneously (S.C.), or intraduodenally (I.D.). Test compounds were screened, *i.e.* changes in gastric volume were measured, usually at 0.63 mg/kg. Other doses and routes were tested if a test compound was shown to be

10 active during the screening procedure. Table C-1 summarizes the mean maximal change in volume on relaxation of the fundus, during the 1 hour observation period after S.C. or I.D. administration of the test compound (0.63 mg/kg).

Table C-1 :

15

Co. No.	Route	Maximum change in volume (ml)	Co. No.	Route	Maximum change in volume (ml)
5	S.C.	41	14	I.D.	144
6	S.C.	146	14	S.C.	90
7	S.C.	34	15	I.D.	5

C.2 Vasoconstrictive activity on basilar artery

Segments of basilar arteries taken from pigs (anaesthetised with sodium pentobarbital) were mounted for recording of isometric tension in organ baths. The preparations were

20 bathed in Krebs - Henseleit solution. The solution was kept at 37°C and gassed with a mixture of 95% O<sub>2</sub> - 5% CO<sub>2</sub>. The preparations were stretched until a stable basal tension of 2 grams was obtained.

The preparations were made to constrict with serotonin (3x10<sup>-7</sup> M). The response to the addition of serotonin was measured and subsequently the serotonin was washed

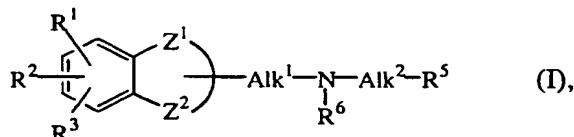
25 away. This procedure was repeated until stable responses were obtained. Subsequently the test compound was administered to the organ bath and the constriction of the preparation was measured. This constrictive response was expressed as a percentage of the response to serotonin as measured previously.

30 The ED<sub>50</sub>-value (molar concentration) is defined as the concentration at which a test compound causes 50% of the constrictive response obtained with serotonin. Said ED<sub>50</sub>-values are estimated from experiments on three different preparations.

-23-

Claims

## 1. A compound of formula (I)



5

a stereochemically isomeric form thereof, an *N*-oxide form thereof, a pharmaceutically acceptable acid addition salt thereof, or a quaternary ammonium salt thereof, wherein

10 Alk<sup>1</sup> is C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkylcarbonylC<sub>1-4</sub>alkyl, carbonyl, carbonylC<sub>1-4</sub>alkyl, or C<sub>1-6</sub>alkanediyl optionally substituted with hydroxy, halo, amino, hydroxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylcarbonyloxy, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy, or C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy;

15 Alk<sup>2</sup> is C<sub>1-4</sub>alkylcarbonylC<sub>1-4</sub>alkyl; C<sub>1-6</sub>alkanediyl substituted with hydroxy, halo, amino, hydroxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy, or C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy; C<sub>3-8</sub>cycloalkanediyl optionally substituted with halo, hydroxy, hydroxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy, or C<sub>3-6</sub>cycloalkylcarbonyloxyC<sub>1-4</sub>alkyloxycarbonyloxy;

20 -Z<sup>1</sup>-Z<sup>2</sup>- is a bivalent radical of formula

-O-CH(R<sup>4</sup>)-CH<sub>2</sub>- (a-1),

-O-CH(R<sup>4</sup>)-CH<sub>2</sub>-O- (a-2),

25 -O-CH(R<sup>4</sup>)-CH<sub>2</sub>-S- (a-3),

-O-CH(R<sup>4</sup>)-CH<sub>2</sub>-CH<sub>2</sub>- (a-4),

-O-CH(R<sup>4</sup>)-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>- (a-5),

-O-C(R<sup>4</sup>)=CH- (a-6),

-O-C(R<sup>4</sup>)=CH-CH<sub>2</sub>- (a-7),

30 -O-C(R<sup>4</sup>)=CH-CH<sub>2</sub>-CH<sub>2</sub>- (a-8), or

-O-CH(R<sup>4</sup>)-CH=CH- (a-9),

wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy;

35 R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently selected from hydrogen, C<sub>1-6</sub>alkyl,

C<sub>3-6</sub>alkenyl, C<sub>1-6</sub>alkyloxy, trihalomethyl, trihalomethoxy, halo, hydroxy,

-24-

5 cyano, nitro, amino, C<sub>1</sub>-6alkylcarbonylamino, C<sub>1</sub>-6alkyloxycarbonyl, C<sub>1</sub>-4alkylcarbonyloxy, aminocarbonyl, mono- or di(C<sub>1</sub>-6alkyl)aminocarbonyl, aminoC<sub>1</sub>-6alkyl, mono- or di(C<sub>1</sub>-6alkyl)aminoC<sub>1</sub>-6alkyl, C<sub>1</sub>-4alkylcarbonyloxy-C<sub>1</sub>-4alkyloxycarbonyloxy, or C<sub>3</sub>-6cycloalkylcarbonyloxyC<sub>1</sub>-4alkyloxy-carbonyloxy; or

when R<sup>1</sup> and R<sup>2</sup> are on adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> taken together may form a bivalent radical of formula

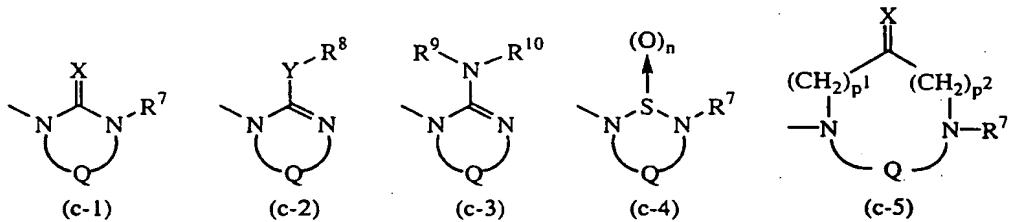
-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-1),	-O-CH <sub>2</sub> -CH <sub>2</sub> -	(b-6),
-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-2),	-O-CH <sub>2</sub> -CH <sub>2</sub> -O-	(b-7),
-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-3),	-O-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-8),
-CH=CH-CH=CH-	(b-4),	-O-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(b-9),
-O-CH <sub>2</sub> -O-	(b-5),		

wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy, C<sub>1</sub>-4alkyl or CH<sub>2</sub>OH;

15 R<sup>4</sup> is hydrogen, C<sub>1</sub>-6alkyl, phenylmethyl, hydroxyC<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkyloxycarbonyl, C<sub>1</sub>-4alkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyl, C<sub>3</sub>-6cycloalkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyloxy, or a direct bond when the bivalent radical -Z<sup>1</sup>-Z<sup>2</sup>- is of formula (a-6), (a-7) or (a-8);

20 R<sup>6</sup> is hydrogen, C<sub>1</sub>-6alkyl, C<sub>1</sub>-4alkylcarbonyl, C<sub>1</sub>-4alkyloxycarbonyl, phenylmethyl, C<sub>1</sub>-4alkylaminocarbonyl, C<sub>1</sub>-4alkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyl, or C<sub>3</sub>-6cycloalkylcarbonyloxyC<sub>1</sub>-4alkyloxycarbonyloxy;

R<sup>5</sup> is a radical of formula



25 wherein n is 1 or 2;

p<sup>1</sup> is 0, and p<sup>2</sup> is 1 or 2; or p<sup>1</sup> is 1 or 2, and p<sup>2</sup> is 0;

X is oxygen, sulfur, NR<sup>9</sup> or CHNO<sub>2</sub>;

Y is oxygen or sulfur;

R<sup>7</sup> is hydrogen, C<sub>1</sub>-6alkyl, C<sub>3</sub>-6cycloalkyl, phenyl or phenylmethyl;

30 R<sup>8</sup> is C<sub>1</sub>-6alkyl, C<sub>3</sub>-6cycloalkyl, phenyl or phenylmethyl;

R<sup>9</sup> is cyano, C<sub>1</sub>-6alkyl, C<sub>3</sub>-6cycloalkyl, C<sub>1</sub>-6alkyloxycarbonyl or aminocarbonyl;

R<sup>10</sup> is hydrogen or C<sub>1</sub>-6alkyl;

-25-

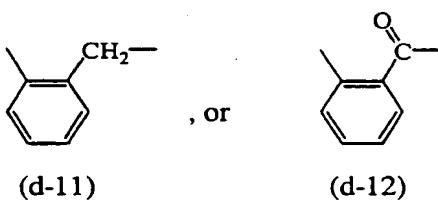
or R<sup>9</sup> and R<sup>10</sup> taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, or morpholinyl group, optionally substituted with C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkyloxy; and

## 5 Q is a bivalent radical of formula

-CH <sub>2</sub> -CH <sub>2</sub> -	(d-1),	-CO-CH <sub>2</sub> -	(d-6),
-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(d-2),	-(CH <sub>2</sub> ) <sub>2</sub> -CO-	(d-7),
-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	(d-3),	-CO-(CH <sub>2</sub> ) <sub>2</sub> -	(d-8),
-CH=CH-	(d-4),	-CO-CH <sub>2</sub> -CO-	(d-9),
-CH <sub>2</sub> -CO-	(d-5),	-CH <sub>2</sub> -CO-CH <sub>2</sub> -	(d-10),

10 -CH<sub>2</sub>-CO- (d-5), -CH<sub>2</sub>-CO-CH<sub>2</sub>- (d-10),  
wherein optionally one or two hydrogen atoms on the same or a different  
carbon atom may be replaced by C<sub>1</sub>-alkyl, hydroxyl or phenyl, or

$\text{O}$  is a bivalent radical of formula



15

2. A compound as claimed in claim 1 wherein R<sup>5</sup> is a radical of formula (c-1) wherein X is oxygen, and Q is a radical of formula (d-2) or (d-5).

20 3. A compound as claimed in claim 1 wherein R<sup>4</sup> is hydrogen; Alk<sup>1</sup> is -CH<sub>2</sub>-, Alk<sup>2</sup> is -CH<sub>2</sub>-CHOH-CH<sub>2</sub>-, R<sup>6</sup> is hydrogen, R<sup>5</sup> is a radical of formula (c-1) wherein X is oxygen, R<sup>7</sup> is hydrogen, and Q is (d-2).

25 4. A compound according to claim 1 wherein R<sup>4</sup> is hydrogen, Alk<sup>1</sup> is -CH<sub>2</sub>-, Alk<sup>2</sup> is -CH<sub>2</sub>-CHOH-CH<sub>2</sub>-, R<sup>6</sup> is hydrogen, R<sup>5</sup> is a radical of formula (c-1) wherein X is oxygen, R<sup>7</sup> is hydrogen, and Q is (d-5).

30 5. A compound according to claim 1 wherein R<sup>4</sup> is hydrogen; Alk<sup>1</sup> is -CHOH-CH<sub>2</sub>-; Alk<sup>2</sup> is -CH<sub>2</sub>-CHOH-CH<sub>2</sub>-; R<sup>6</sup> is hydrogen; R<sup>5</sup> is a radical of formula (c-1) wherein X is oxygen, R<sup>7</sup> is hydrogen, and Q is (d-2)

35 6. A compound according to claim 1 wherein the compound is 1-[3-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]- 2-hydroxypropyl]-2,4-imidazolidinedione; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

-26-

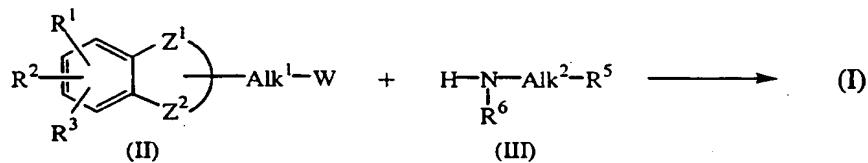
7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 6.

5 8. A process for preparing a pharmaceutical composition as claimed in claim 7 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.

9. A compound as claimed in any of claims 1 to 6 for use as a medicine.

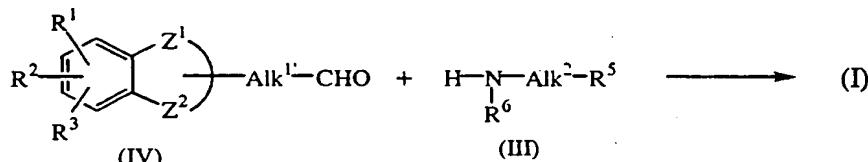
10 10. A process for preparing a compound of formula (I) wherein

a) an intermediate of formula (II) is alkylated with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base,



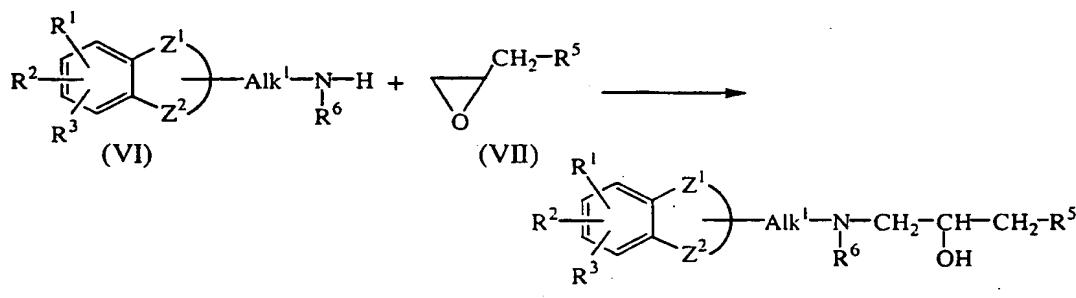
15

b) an intermediate of formula (IV), wherein Alk<sup>1</sup> represents a direct bond or C<sub>1</sub>-5alkanediyl, is reductively alkylated with an intermediate of formula (III);



20

c) an intermediate of formula (VI) is reacted with an intermediate of formula (VII) thus yielding compounds of formula (I-a), defined as compounds of formula (I) wherein Alk<sup>2</sup> represents -CH<sub>2</sub>-CHOH-CH<sub>2</sub>-;



25

(I-a)

-27-

in the above reaction schemes the radicals -Z<sup>1</sup>-Z<sup>2</sup>-, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, Alk<sup>1</sup> and Alk<sup>2</sup> are as defined in claim 1 and W is an appropriate leaving group;

5

- d) or, compounds of formula (I) are converted into each other following art-known transformation reactions; or if desired; a compound of formula (I) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/EP 00/04746

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D405/12 C07D417/12 A61K31/4164 A61P9/08

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 17017 A (JANSSEN) 2 September 1993 (1993-09-02) cited in the application claims; tables 1-4 -----	1-3,6-9
P,A	WO 99 29687 A (JANSSEN) 17 June 1999 (1999-06-17) the whole document -----	1,2,7-10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

16 November 2000

Date of mailing of the international search report

24/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenttaan 2  
NL - 2260 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No  
PCT/EP 00/04746

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9317017	A 02-09-1993	AP 416 A		29-09-1995
		AT 138064 T		15-06-1996
		AU 3499193 A		13-09-1993
		BG 62052 B		29-01-1999
		BG 98870 A		31-03-1995
		CA 2117483 A		02-09-1993
		CN 1079470 A, B		15-12-1993
		CZ 9402020 A		18-01-1995
		DE 69302687 D		20-06-1996
		DE 69302687 T		14-11-1996
		DK 639192 T		19-08-1996
		EP 0639192 A		22-02-1995
		ES 2087721 T		16-07-1996
		FI 943928 A		26-08-1994
		GR 3019927 T		31-08-1996
		HR 930235 A		31-10-1997
		HU 71129 A		28-11-1995
		HU 9500317 A		28-09-1995
		IL 104868 A		04-01-1998
		JP 2779268 B		23-07-1998
		JP 7504408 T		18-05-1995
		KR 190300 B		01-06-1999
		LT 3049 B		25-10-1994
		LV 10715 A		20-06-1995
		LV 10715 B		20-12-1995
		MX 9301053 A		31-03-1994
		NO 943186 A		29-08-1994
		NZ 249124 A		28-08-1995
		PL 174736 B		30-09-1998
		RO 115630 B		28-04-2000
		RU 2121999 C		20-11-1998
		SG 47763 A		17-04-1998
		SI 9300097 A		30-09-1993
		SK 102994 A		11-07-1995
		US 5541180 A		30-07-1996
		US 5624952 A		29-04-1997
		US 5607949 A		04-03-1997
		US 5688952 A		18-11-1997
		ZA 9301404 A		26-08-1994
WO 9929687	A 17-06-1999	AU 2412799 A		28-06-1999
		BR 9814256 A		03-10-2000
		EP 1036073 A		20-09-2000
		NO 20002074 A		02-06-2000
		US 6133277 A		17-10-2000